M E M O R A N D U M

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

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To: File (**STN 125284/0**)

From: Nisha Jain

APPROVED
By Nisha Jain at 2:45 pm, Aug 20, 2008

Subject: **Recommendation to grant GTC Biotherapeutics request for Priority Review for their BLA for Antithrombin III (recombinant)**

Through: Toby Silverman, M.D.
Chief, Clinical Review Branch/ Division of Hematology

CC: Pratibha Rana

It is to recommended that FDA grant GTC Biotherapeutics request for Priority Review for their original biologics license application (BLA) for Antithrombin III (recombinant) since it meets the requirements for Priority Review as specified in *Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review*. If you concur with the recommendation, this BLA, which was submitted on August 8, 2008, will be reviewed under a 6-month review schedule.

BACKGROUND

Antithrombin III (recombinant) has been designated a product for Fast Track development. It has an orphan drug designation for the prevention of thromboembolic events during high risk situations such as surgery and pregnancy in hereditary antithrombin III deficient patients.

CRITERIA TO QUALIFY FOR PRIORITY REVIEW

I. Antithrombin III (recombinant) is intended to treat a serious condition:

1. Congenital Antithrombin (AT) III deficiency is an autosomal dominant disorder. It is characterized by either a reduction in antithrombin III (type I) or the presence of a dysfunctional form (type II). Deficiency of antithrombin III leads to hypercoagulability, potentially resulting in thromboses in the veins of the extremities, as well as in the mesenteric, renal, hepatic and portal veins and vena cava. A life-threatening complication of pulmonary embolism may also occur.

2. Thromboembolic events in congenital AT deficient patients are uncommon prior to puberty but increase thereafter, particularly during periods of high risk, such as pregnancy, surgery, or prolonged bed rest. Congenital AT deficiency causes a life-long increased risk of venous thromboembolism and up to 70% of cases develop a venous thromboembolic event (VTE) during their lives. Often these are recurrent and may be life-threatening. Failure to properly treat congenital AT deficient patients especially during high risk situations such as surgery, trauma or pregnant women during the peri-partum period may result in VTEs. The risk of development of VTEs as compared to the normal population in these situations is increased by a factor of 10-50. VTEs may lead to death from life-threatening pulmonary emboli or may have other life-long sequelae.

II. Antithrombin III (recombinant has the potential to address unmet medical needs:

Currently, the only available treatment of congenital AT patients in high risk situation is administration of human plasma derived antithrombin III, Thrombate III® (manufactured by Talecris Biopharmaceuticals) alone or in conjunction with heparin. The availability of the Thrombate III® has been unpredictable and intermittent. During the period when Thrombate III® was not available, GTC's Antithrombin IIII, recombinant was made available to patients on a compassionate use basis. GTC may establish through use of recombinant DNA technology, a continuous, unconstrained supply of antithrombin III which may be made available to patients, ensuring continuous availability of product.

Thrombate III®, due to the fact that it is derived from human plasma, carries warning about the potential risk of transmission of known and unknown infectious agents. This type of warning may not be needed for GTC's ATIII product because it is manufactured by a recombinant technology.

RECOMMENDATION

Based on the reasons listed above, we find that GTC Biotherapeutics, Antithrombin III (recombinant) meets the criteria as stated in *Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review*: (1) It is intended to treat a serious condition, and (2) it has the potential to address unmet medical needs. Also, this product has the ability to provide benefits similar to those of alternatives but with improvement in some factors such as compliance or convenience that will be shown to lead to favorable effect on serious outcome.

Therefore, we recommend that GTC's request for Priority Review for the BLA of Antithrombin III (Recombinant) be granted.